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EXAMINER	
PAPPU, SITA S	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/814,047	WAKAMATSU ET AL.	
	Examiner	Art Unit	
	Sita Pappu	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment filed on July 16, 2001 in paper #4 has been entered. Claim 6 is amended. Claims 1-22 are, currently, pending in the instant application. This paper contains an examination of claims 1-22 on their merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the claims 1-22 are directed to a see-through medaka produced by a method that is not readily reproducible. The medaka of the instant invention were produced by repeated selective mating between the parental strains of medaka for producing the next generation of medaka. This type of repeated selective matings are not exactly reproducible every time a medaka of the instant invention needs to be produced, because the applicants disclose that for selective mating in each generation, individuals of desired phenotype or genotype were selected and mated to produce the next generation (see page 6 of the Specification, last paragraph). The shuffling of genetic material that occurs during mating is random, so the genetic make up of the organism differs with each trial of mating to produce the medaka of the instant invention. Therefore, without a biological deposit, the invention does not satisfy the 'how to make 'requirement, since the medaka of the instant invention is not reproducible. A biological deposit, under the terms of the Budapest Treaty, can be made to satisfy the "how to

make" requirement, thereby enabling the invention. The specification on pages 7, 13, 15, 19, 23, 24, 26, 31, 34, 35, and 38 discloses that biological deposits were made but fails to specify that they were made under the terms of the Budapest Treaty. If the deposits were made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific plasmids and the medaka strains have been deposited under the Budapest Treaty and that the plasmids and the medaka strains will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and,

(d) a test of the viability of the biological material was performed at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become inviable.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a see-through medaka which is deficient in iridophores, melanophores, xanthophores and leucophores, wherein the said deficiency is a result of repeated mating between iridophore deficient mutant medaka strain 'gu', albino mutant medaka strain 'i-3' and leucophore deficient mutant medaka strain 'lf' and further selective mating between the resulting medaka and iridophore deficient mutant medaka strain 'il-1', does not reasonably provide enablement for any see-through medaka which is deficient in iridophores, melanophores, xanthophores and leucophores wherein the deficiency is a result of any number and type of mutations in the genes involved in the pigmentation pathways in the genome of medaka. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the medaka over the full scope of the claims.

Claims 1-3 encompass any see-through medaka which is deficient in iridophores, melanophores, xanthophores and leucophores. The specification discloses only a see-through medaka which is deficient in iridophores, melanophores, xanthophores and leucophores, wherein the said deficiency is a result of repeated mating between iridophore deficient mutant medaka strain 'gu', albino mutant medaka strain 'i-3' and leucophore deficient mutant medaka strain 'lf' and further selective mating between the resulting medaka and iridophore deficient mutant medaka strain 'il-1'.

In the instant case, claims 1-3 are drawn to a see-through medaka which is deficient in iridophores, melanophores, xanthophores and leucophores. Claims 1-3 encompass any see-through medaka which is deficient in the said pigments, wherein the deficiency is a result of any number and types of mutations in the genes involved in the pigmentation pathways in the genome of medaka thereby covering any and all mutant forms, substitutions, deletions, or insertions in the genes involved. The specification only teaches a see-through medaka which is deficient in the said pigments, wherein the said deficiency is a result of repeated mating between iridophore deficient mutant medaka strain 'gu', albino mutant medaka strain 'i-3' and leucophore deficient mutant medaka strain 'lf' and further selective mating between the resulting medaka and iridophore deficient mutant medaka strain 'il-1' in case of claims 1-3. The specification does not teach how to make and use the medaka of the instant case with any and all types and number of mutations that result in the specified phenotype, as claimed in the claims. The specification does not teach the specific genetic mutations that result in the medaka that are deficient in the said pigments, other than those used in the selective matings to produce the medaka of the claimed invention. For example, Ozato et al. (1994; Develop. Growth. And Differ., vol. 36, no. 5, pp437-443) disclose that 49 color mutants of medaka are maintained and available at the Nagoya University, and that most of them are autosomal recessive (page 437, right column, subsection on 'mutagenesis, spontaneous mutants, lines 11-13) and that no linkage has been found among mutant genes in medaka (page 438, right column, subsection 'linkage maps', lines 1-2). In the absence of specific guidance, it is unpredictable how these various

color mutations would be inherited and what the resulting phenotype would be, for one of skill in the art to select the parents for each, successive generation of selective mating such that a skilled artisan would arrive at the see-through medaka of the present invention, using any and all of the color mutants of medaka that are available. The breadth and scope of claims 1-3, thus, surpass that enabled by the specification. Even though the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention as claimed. The specification and the working examples provide sufficient guidance to practice the invention with only a see-through medaka which is deficient in iridophores, melanophores, xanthophores and leucophores, wherein the said deficiency is a result of repeated mating between iridophore deficient mutant medaka strain 'gu', albino mutant medaka strain 'i-3' and leucophore deficient mutant medaka strain 'lf' and further selective mating between the resulting medaka and iridophore deficient mutant medaka strain 'il-1' in the case of claims 1-3. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all mutations of the types claimed.

Thus, the specification is not enabling for any see-through medaka which is deficient in iridophores, melanophores, xanthophores and leucophores wherein the deficiency is a result of any number and type of mutations in the genes involved in the pigmentation pathways in the genome of medaka. Therefore, based on the lack of guidance in the specification as to how to make the invention with any color mutant of

medaka as the parental strain in each generation of selective mating, such that one of skill in the art would arrive at the see through medaka of the claimed invention, and the breadth of the claims, it would have required undue experimentation for the skilled artisan at the time of filing to practice the full scope of the claimed invention.

Claims 4-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a see-through medaka which is deficient in iridophores, melanophores, xanthophores, wherein the said deficiency is a result of repeated mating between iridophore deficient mutant medaka strain 'gu', albino mutant medaka strain 'I-3' and leucophore deficient mutant medaka strain 'lf' and medaka FLF strain which is deficient in leucophores in the female, and thereby allowing the identification of the sex of said medaka by the presence or absence of leucophores and/or a DNA marker, SL1, does not reasonably provide enablement for any see-through medaka which is deficient in iridophores, melanophores, xanthophores wherein the deficiency is a result of any number and type of mutations in the genes involved in the pigmentation pathways in the genome of medaka. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 4-6 encompass any see-through medaka which is deficient in iridophores, melanophores, xanthophores. The specification discloses only a see-through medaka which is deficient in iridophores, melanophores, xanthophores, wherein the said deficiency is a result of repeated mating between iridophore deficient mutant medaka

strain 'gu', albino mutant medaka strain 'I-3' and leucophore deficient mutant medaka strain 'lf' and medaka FLF strain which is deficient in leucophores in the female, and thereby allowing the identification of the sex of said medaka by the presence or absence of leucophores and/or a DNA marker.

In the instant case, the claims 4-6 are drawn to a see-through medaka which is deficient in iridophores, melanophores, xanthophores and deficient in leucophores only in females. Claims 4-6 encompass any see-through medaka which is deficient in the said pigments, wherein the deficiency is a result of any number and types of mutations in the genes involved in the pigmentation pathways in the genome of medaka thereby covering any and all mutant forms, substitutions, deletions, or insertions in the genes involved. The specification only teaches a see-through medaka which is deficient in the said pigments, wherein the said deficiency is a result of repeated mating between iridophore deficient mutant medaka strain 'gu', albino mutant medaka strain 'i-3' and leucophore deficient mutant medaka strain 'lf' and medaka FLF strain which is deficient in leucophores in the female, and thereby allowing the identification of the sex of said medaka by the presence or absence of leucophores and/or a DNA marker, SL1. The specification does not teach how to make and use the medaka of the instant case with any and all types and number of mutations that result in the specified phenotype, as claimed in the claims. The specification does not teach the specific genetic mutations that result in the medaka that are deficient in the said pigments, other than those used in the selective matings to produce the medaka of the claimed invention. For example, Ozato et al. (1994; Development, Growth And Differentiation, vol. 36, no. 5, pp437-443)

disclose that 49 color mutants of medaka are maintained and available at the Nagoya University, and that most of them are autosomal recessive (page 437, right column, subsection on 'mutagenesis, spontaneous mutants, lines 11-13) and that no linkage has been found among mutant genes in medaka (page 438, right column, subsection 'linkage maps', lines 1-2). In the absence of specific guidance, it is unpredictable how these various color mutations would be inherited and what the resulting phenotype would be, for one of skill in the art to select the parents for each, successive generation of selective mating such that a skilled artisan would arrive at the see-through medaka of the present invention, using any and all of the color mutants of medaka that are available. The breadth and scope of claims 4-6, thus, surpass that enabled by the specification. Even though the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention as claimed. The specification and the working examples provide sufficient guidance to practice the invention with only a see-through medaka which is deficient in iridophores, melanophores, xanthophores, wherein the said deficiency is a result of repeated mating between iridophore deficient mutant medaka strain 'gu', albino mutant medaka strain 'i-3' and leucophore deficient mutant medaka strain 'lf' and medaka FLF strain which is deficient in leucophores in the female, and thereby allowing the identification of the sex of said medaka by the presence or absence of leucophores and/or a DNA marker, SL1, in the case of claims 4-6. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all mutations of the types claimed. Thus the

specification is not enabling for any see-through medaka which is deficient in iridophores, melanophores, xanthophores and deficient in leucophores only in females, wherein the deficiency is a result of any number and types of mutations in the genes involved in the pigmentation pathways in the genome of medaka.

Therefore, based on the lack of guidance in the specification as to how to make the invention with any color mutant of medaka as the parental strain in each generation of selective mating, such that one of skill in the art would arrive at the see through medaka of the claimed invention, and the breadth of the claims, it would have required undue experimentation for the skilled artisan at the time of filing to practice the full scope of the claimed invention.

Claims 7-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic see-through medaka wherein a specific organ is allowed to produce luminescence by introducing a hybrid gene which is a fusion of an olvas gene promoter, that expresses specifically in the gonadal organ of said medaka, operably linked to a coding region of a gene encoding a green fluorescent protein, does not reasonably provide enablement for any see-through medaka containing any hybrid gene being fusion of any organ-specific promoter with a coding region of a gene encoding any fluorescent protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 7-22 encompass any see-through medaka wherein any organ is allowed to produce luminescence by introducing any hybrid gene which is a fusion of any promoter specific to any organ with a coding region of a gene encoding any fluorescent protein. The specification discloses only a transgenic see-through medaka wherein a specific organ is allowed to produce luminescence by introducing a hybrid gene which is a fusion of an olvas gene promoter, that expresses specifically in the gonadal organ of said medaka, operably linked to a coding region of a gene encoding a green fluorescent protein. The specification does not disclose a variety of organ-specific promoters, nor does it disclose a variety of hybrid genes operably linked to a variety of organ-specific promoters. The specification only discloses an olvas promoter which is specific to the gonadal organ of medaka, that is operably linked to a green fluorescnt protein.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

In the instant case, the claims 7-22 are drawn to a see-through medaka wherein a specific organ is allowed to produce luminescence by introducing a hybrid gene which

is a fusion of a promoter specific to an organ with a coding region of a gene encoding a fluorescent protein. Claims 7-22 encompass any see-through medaka wherein any organ is allowed to produce luminescence by introducing any hybrid gene which is a fusion of any promoter specific to any organ with a coding region of a gene encoding any fluorescent protein. The specification only teaches a transgenic see-through medaka wherein a specific organ is allowed to produce luminescence by introducing a hybrid gene being a fusion of an olvas gene promoter, which expresses specifically in the gonadal organ of said medaka, with a coding region of a gene encoding a green fluorescent protein. The specification does not teach how to make and use the medaka of the instant case with any and all types of hybrid genes, and promoters as claimed in the claims. The specification does not disclose a variety of organ-specific promoters, nor does it disclose a variety of hybrid genes operably linked to a variety of organ-specific promoters. The specification only discloses an olvas promoter which is specific to the gonadal organ of medaka, that is operably linked to a green fluorescnt protein. The breadth and scope of claims 7-22, thus surpass that enabled by the specification. Even though the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention as claimed. The specification and the working examples provide sufficient guidance to practice the invention with only a transgenic see-through medaka wherein a specific organ is allowed to produce luminescence by introducing a hybrid gene being a fusion of a olvas gene promoter, which expresses specifically in the gonadal organ of said medaka, with a coding region of a gene

encoding a green fluorescent protein. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all hybrid genes. Further, Linney etv al. (1999; Developmental Biology, vol. 213, no. 1, pp. 207-216) state that even though GFP could be a valuable reporter gene, the stability of GFP can create problems in the interpretation and use of it as a reporter in systems that develop rapidly (page 215, left column, lines 5-11), and that GFP genes with reduced stability might be more useful in studies of transgenic fish (page 215, left column, lines 20-24). Thus, it is unpredictable how transgenic medaka containing different hybrid GFP genes would behave in terms of the expression of GFP in the germ cells and how different promoter constructs would affect the GFP expression.

Although working examples are not required, particularly in the predictable arts, the presence or absence of working examples is one factor that must be considered, particularly in the unpredictable arts. It is noted that the law requires that the disclosure of an application shall inform those skilled in the art how to use applicants' alleged discovery, not how to find out how to use it for themselves (see In re Gardner et al. 166 USPQ 138 (CCPA 1970). The specification only teaches what is intended to be done, but does not actually teach how to do that which is intended. Thus, the specification is not enabling for any see-through medaka containing any hybrid gene being fusion of any organ-specific promoter with a coding region of a gene encoding any fluorescent protein.

Therefore, based on the lack of guidance in the specification as to how to use the invention with any hybrid gene fused to any promoter, and the breadth of the claims, it

would have required undue experimentation for the skilled artisan at the time of filing to practice the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 7-22 are rejected under 35 U.S.C. 102(a) as being anticipated by Tanaka et al. (Proceedings of the National Academy of Sciences, vol. 98, no.5, pp2544-2549, February 27, 2001).

Tanaka et al. (2001) teach a transgenic medaka which expresses the green fluorescent protein exclusively in germ cells (see abstract, page 2544). The transgenic medaka of Tanaka et al. (2001) contains a construct wherein the medaka vasa gene promoter, which is referred to as olvas promoter, is operably linked to the green fluorescent protein gene, and allows for the expression of the green fluorescent protein in the gonadal cells of the transgenic medaka (page 2545, left column, paragraph 2). The transgenic medaka of Tanaka et al. (2001) lacks most pigments and is transparent (page 2548, right column, lines 2-4), allowing easy observation of GFP fluorescence in live specimens.

Thus, Tanaka et al. (2001) anticipated the transgenic medaka of claims 7-22.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (703) 305 1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746 7442 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-2982.

Anne-marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER

S. Pappu
January 25, 2002